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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/000,433 | 11/30/2001 | Kazuma Tomizuka | 014643-012110US | 9190 |

7278 7590 12/28/2004

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| EXAMINER |
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LI, QIAN JANICE

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| ART UNIT | PAPER NUMBER |
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1632

DATE MAILED: 12/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/000,433

Applicant(s)

TOMIZUKA ET AL.

Examiner

Q. Janice Li

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 September 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,6-9 and 11 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,6-9 and 11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 30 November 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

The amendment and response filed 9/27/04 has been entered. Claim 2 has been canceled. Claim 1 has been amended. Claims 1, 6-9, and 11 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 9/27/04 response would be addressed to the extent that they apply to current rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 8, 9, and 11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Lonberg et al* (US 5,770,429), in view of *Tomizuka et al* (Nat Genetics 1997;16:133-43 and PNAS 2000 Jan;97:722-7), for reasons of record and

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following, particularly because these claims encompass a transgenic mouse without inactivation of endogenous Ig heavy and light chain loci.

Applicants first argue that creating a mouse that contained a transchromosome yield unexpected results for expressing the human Ig heavy and light chain genes, and pointing to the specification pages 28, examples 5, 6, and 7).

In response, it is noted that examples 5-7 use cross-bred mice as described in example 3, which was homozygous for inactivation mutations of the endogenous heavy chain locus (CM2D) and kappa light chain locus (CKD). Page 28 of the specification particularly pointed out in order to achieve improved stability of the human kappa light chain locus, the human kappa light chain locus transgene Kco5 was combined with the stable hCF(SC20) transchromosome together with functional inactivation mutations of the endogenous mouse heavy and kappa light chain loci. The specification fails to teach that the unexpected results could also be obtained in mice having active endogenous mouse heavy and kappa light chain loci. Accordingly, the unexpected results do not apply to those mice. The court has determined, "WHETHER THE UNEXPECTED RESULTS ARE THE RESULT OF UNEXPECTEDLY IMPROVED RESULTS OR A PROPERTY NOT TAUGHT BY THE PRIOR ART, THE "OBJECTIVE EVIDENCE OF NONOBVIOUSNESS MUST BE COMMENSURATE IN SCOPE WITH THE CLAIMS WHICH THE EVIDENCE IS OFFERED TO SUPPORT." IN OTHER WORDS, THE SHOWING OF UNEXPECTED RESULTS MUST BE REVIEWED TO SEE IF THE RESULTS OCCUR OVER THE ENTIRE CLAIMED RANGE. *IN RE CLEMENS*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)" ((MPEP 716.02(d), emphasis added)).

Applicants then argue that the motivations to combine references pointed out in the previous Office action does not provide necessary motivation because 1) the

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antibody isotype selection is uncontrollable in the transgenic mouse having the V region cloned into the desired constant region; 2) the greatest diversity arises from the double transchromosomal mice; and 3) the levels of antibody production is irrelevant because Abs are produced typically in recombinant expression systems in vitro.

The arguments have been fully considered but found not persuasive for reasons of record and because the reasoning works against Applicants' own teaching.

For example, before the discovery of transgenic mice carrying transmittable transchromosome, Applicants have obtained numerous patents drawn to transgenic mice capable of producing heterologous human immunoglobulins using affinity tagging selecting for switched isotypes. If the antibody isotype selection is uncontrollable, then it is unclear how these patents worked. On the second argument, the greatest diversity may arise from the double transchromosomal mice, the instant claims are drawn to a single transchromosomal mice with the human light chain locus carried by a transgene integrated into the genome of said mouse, the claims are not drawn to a double transchromosomal mouse. On the third argument, it is the applicant who teaches the relevance of transgenic mice and the levels of antibody production. As indicated in the previous Office action, the cited '429 patent teaches, "BECAUSE EACH TRANSGENIC LINE MAY REPRESENT A DIFFERENT SITE OF INTEGRATION OF THE TRANSGENE, AND A POTENTIALLY DIFFERENT TANDEM ARRAY OF TRANSGENE INSERTS, AND BECAUSE EACH DIFFERENT CONFIGURATION OF TRANSGENE AND FLANKING DNA SEQUENCES CAN AFFECT GENE EXPRESSION, IT IS PREFERABLE TO IDENTIFY AND USE LINES OF MICE THAT EXPRESS HIGH LEVELS OF HUMAN IMMUNOGLOBULINES..."

(*Lonberg et al*, column 35, lines 28-43). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to breed the mice as taught

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by *Lonberg et al*, and *Tomizuka et al et al*, to produce a new line of mice expressing different antibody isotope or diversity, or having a higher level of antibody production with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the crossbreeding would facilitate the production of transgenic mice in variety as well as amount of antibodies. Thus, the claimed invention as a whole was *prima facie* obvious, and the rejection stands.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730.

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The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

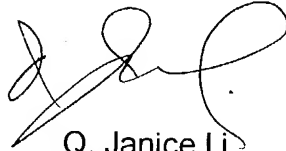
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Q. Janice Li
Primary Examiner
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December 20, 2004